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A Review on the Application of Stem Cell Exosomes in Anti-aging

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Abstract. A significant biomedical concern is skin aging, which is caused by both extrinsic environmental stressors like UV radiation and intrinsic genetic factors. Traditional anti-aging treatments usually offer only superficial or temporary benefits, failing to deliver long-lasting effects to help skin recover from aging. Exosomes generated from mesenchymal stem cells (MSCs) have recently become a promising cell-free treatment due to their significant regeneration potential, low immunogenicity, and molecular regulation of target cells. This review summarizes how stem cell-derived exosomes combat skin aging across three key mechanisms: anti-oxidation, anti-inflammation, and tissue repair. Exosomes deliver bioactive molecules, including miRNAs and antioxidant enzymes, that clear reactive oxygen species (ROS); activate endogenous defenses like the Keap1-Nrf2 pathway; and suppress chronic inflammation by modulating NF-κB. All of them give skin cells more time to recover and delay the process of aging. While experimental findings are encouraging, key hurdles remain, mainly because existing methodsstill lack robust human clinical data. This review outlines both the potential and current limitations of exosome therapies to help guide future research toward standardized, clinically viable anti-aging solutions.

Keywords: Mesenchymal stem cell exosomes, Skin aging, Antioxidation, Tissue repair

1. Introduction

Skin aging is an inevitable biological process that everyone would meet with aging, which is driven by gene regulation and hormonal changes. In addition, with external factors like ultraviolet radiation or even environmental changes could accelerate the process. As the quality of life is ensured for more and more people and with the human's nature of pursuing beauty, dealing with skin aging has been a popular topic around the world. Furthermore, as the global population ages and public awareness of caring for the skin health increases, delaying skin aging has become a biomedical priority for a majority of scientists. The use of stem cells, one of the safe anti-aging techniques, is encouraged by the growing need for a way to slow down the aging process.

Exosomes are nanoscale extracellular vesicles that carry different bioactive molecules including lipids, proteins, and various RNAs. They play an essential role in intercellular communication. Among different sources, mesenchymal stem cell-derived exosomes have attracted scientists to pay attention, since they have low immunogenicity, easy accessibility, and strong regenerative potential. The stem cell-derived exosome has been widely used in a variety of cosmetic products, including

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face creams, serums, and masks, and it shows unmatched advantages over traditional therapies in activating the skin's endogenous regeneration mechanism, according to Jin and Jin noted [1].

Unlike traditional stem cell ingredients such as antioxidants that work through surface production or direct application on skin surface. Recent research has shown that by improving the activity of aged dermal fibroblasts, extracellular vesicles produced from mesenchymal stem cells can postpone skin aging processes [2]. Stem-cell derived exosomes could regulate the target cells at the molecular level, which could offer a fundamentally and ultimately improve the situation of skin-aging.

Mesenchymal stem cell-derived exosomes have been investigated as essential elements of regenerative therapy [3]. Building on this foundation, recent studies have further explored the role of MSC-derived exosomes in skin anti-aging. Researchers have investigated their effects on different aspects of aged skin, including anti-oxidation, anti-inflammation, and skin tissue repair. Although the specific experimental models and outcomes vary across studies, all the studies offer evidence that MSC-derived exosomes could provide a promising approach that help delay or even reverse skin aging.

Although there has been existed a majority of anti-aging products on the market, most common approaches suffer from limitations such as skin irritation, short-term effects, or an inability to fundamentally reverse cellular aging. Therefore, systematically reviewing on the current understanding and process of how those exosomes could help with delaying skin aging is essential for guiding future exploitation on new approaches and practical application. This review aims to summarize recent advances in the anti-aging mechanisms of especially stem cell exosomes from anti-oxidation, anti-inflammation, and skin tissue repair.

2. Skin aging mechanisms and exosome fundamentals

2.1. Mechanism of skin aging

As reviewed by Makrantonaki and Zouboullis, skin aging is a multifactorial process driven by the combined effects of intrinsic and extrinsic factors. Intrinsic aging, which is also known as chronological aging, is genetically determined and occurs naturally even only with the passage of time. For example, with sun-protected skin, where aging is primarily driven by intrinsic factors, the epidermis gradually thins with age and may decrease in thickness by approximately 10–50% between the ages of 30 and 80 years. Compared with photoaged skin, intrinsically aged (sun-protected) skin generally exhibits less severe structural changes in the dermis, but gradually and gentle changes [4].

As skin undergoes intrinsic aging, age-related changes in the dermis include extracellular matrix deterioration and reduced fibroblast abundance, leading to impaired tissue maintenance and remodeling capacity [4]. Moreover, aging skin fibroblasts reduce extracellular matrix formation, particularly that of the main components of the collagen network, such as collagen types I and III [5] The decline in collagen production directly contributes to reduced fibroblast activity and loss of skin elasticity. Age-related alterations in the structure and function of elastic fibres are the main reasons for the loss of skin elasticity, making elastic fibre deterioration a key feature of dermal aging [6]. Together, these changes lead to the development of visible signs of skin aging.

At the molecular level, several interconnected mechanisms drive intrinsic skin aging. One key pathway involves telomere biology. Telomere dysfunction contributes to skin aging, where mice with increased TRF2 expression show accelerated telomere degradation and premature skin deterioration [7]. Cellular senescence is another significant aspect. Wrinkles and elastic morphological changes are associated with the quantity of p16INK4a positive cells, a recognized

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indicator of cellular senescence. Furthermore, an important regulatory mechanism involves fibroblast growth factors (FGFs), which maintain skin homeostasis by regulating fibroblast proliferation, extracellular matrix remodeling, and tissue repair. Age-related alterations in FGF signaling have been implicated in the progression of skin aging, making these pathways promising therapeutic targets [8]. While intrinsic aging is inevitable, its progression can be accelerated by external factors discussed in the following section.

2.2. Exosome isolation and characterization

Significant challenges remain in exosome isolation and characterization due to their small size (30–150 nm) and low density, which often results in co-purification with cell fragments and proteins from biofluids [9]. Especially the small size and mixed nature of exosomes, and the complexity of biological fluids make it very difficult to isolate and purify exosomes without contamination from proteins, cell debris, and other types of extracellular vesicles [9].

Researchers have developed a variety of isolation methods, such as polymer-based precipitation, size-exclusion chromatography, and ultracentrifugation, to solve these problems [10]. Ultracentrifugation utilizes density differences between the exosomes and other contaminating materials within the sample as well as differences in their size to separate them. However, there are trade-offs involved with using these methods (i.e. level of purity, amount of isolated material and simplicity of use) and should therefore be carefully taken into consideration before proceeding onto downstream research. After isolation, the exosomes have to be characterized by multiple biophysical techniques. TEM is used to observe the characteristic cup-shape and the bilayer structure of the exosomes. NTA or DLS can be used to measure the size distribution of the nanoparticles and thereby determine if the isolated vesicles fall within the normal range of 30-150 nm in diameter.

3. Mechanisms of stem cell-derived exosomes in skin anti-aging

3.1. Anti-oxidative stress

The aging of the skin seems to be connected to the buildup of ROS (reactive oxygen species), which are the cause of damage to many of the cell components, including biomolecules such as proteins, lipids and DNA. According to how special the effect that oxygen brought to skin is, the way to mitigate oxidative stress is a critical strategy for combating skin aging. As Rinnerthaler et al. mentioned, oxidative stress is widely recognized as a major contributor to skin aging, with ROS driving age-related changes in the skin more extensively than in most other organs [11]. Consequently, therapeutic strategies that reduce oxidative stress and restore redox balance have emerged as a critical strategy for combating skin aging that is approaching for preventing and treating skin aging [11].

Among these emerging therapeutic strategies, stem cell-derived exosomes have attracted increasing attention becasue stem cell-derived exosomes help mitigate oxidative stress. The process of discovering exosomes' function already had huge progress: evidence from animal models indicates that exosomes possess antioxidant properties through four main pathways [12]. First, they could direct reduction of excessive reactive oxygen species (ROS). Second, their could promote intracellular anti-oxidative stress defence. Third, they suppress the modulation of immune responses through inhibition of ROS overproduction and alter the mitochondrial performance. Antioxidant enzymes like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) are directly carried by exosomes and instantly lower ROS levels in recipient cells. For instance, Gui et

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al. showed that exosomes produced from human umbilical cord mesenchymal stem cells (HuMSC-Exos) reduce UVB-induced oxidative stress in skin cells by releasing miR-200a-3p, which boosts endogenous antioxidant responses and activates the Keap1-Nrf2 signaling pathway [13].

3.2. Anti-inflammation

Chronic inflammation is an essential driver of both aging and impaired wound healing. Persistent activation of nuclear factor NF-κB signaling promotes the production of pro-inflammatory cytokines, creating an inflammatory microenvironment that disrupts tissue homeostasis and delays skin repair [14]. This creates the critical environment that suppresses the repair process for skin. In particular, MSC-derived extracellular vesicles containing miR-146a have been shown to suppress Th1-mediated inflammatory responses through regulation of the AKT/NF-κB pathway, resulting in reduced expression of pro-inflammatory cytokines such as TNF-αand IFN-γ [15]. Furthermore, MSC-derived exosomal miRNAs may also counteract inflammation associated with cellular senescence, as senescent cells release inflammatory mediators through the senescence-associated secretory phenotype (SASP), contributing to inflammaging and impaired tissue repair [14]. They show how important exosomes could be in such different pathways.

The anti-inflammatory potential of exosomes derived from MSCs is not only supported by the experimental model but also by their clinically relevant skin diseases, which share common pathways with skin aging. By lowering clinical severity, serum IgE levels, eosinophil accumulation, and immune cell infiltration in skin lesions, Matwiejuk et al. showed that exosomes produced from adipose-derived mesenchymal stem cells (ADMSC) reduce inflammation associated with atopic dermatitis [16]. MSC-Exo-miRNAs contribute to the creation of a molecular environment that promotes both effective skin regeneration and healthy aging by influencing core transcriptional pathways and guiding macrophage phenotypic transitions thru cytokine network modulation.

4. Conclusion

Collagen degradation, persistent inflammation, and poor tissue regeneration are all consequences of the complex and unavoidable process of skin aging, which is fueled by both internal and external factors. While traditional anti-aging interventions have shown very limited efficacy, stem cell-derived exosomes that were invented today have become a promising cell-free therapeutic strategy. Unlike traditional approaches, exosomes regulate target cells at the molecular level, offering a more efficient, convenient and cutting-edge mechanism for combating skin aging.

The review summarizes the anti-aging mechanisms of stem cell-derived exosomes from 3 perspectives. Anti-oxidation, exosomes directly scavenge reactive oxygen species and activate different pathways to improve the production of antioxidant enzymes, like SOD and CAT. Regarding anti-inflammation, exosomal miRNAs suppress a central inflammatory pathway (NF-κB) by targeting its upstream activators, thereby reducing the production of key inflammatory signals. These microRNAs also promote the shift of immune cells from a pro-inflammatory state to a tissue-repairing state.

Several limitations of this review should be acknowledged. First, the discussion focuses primarily on skin aging, without delving into other aging-related mechanisms such as telomere attrition or epigenetic modifications. Second, much of the evidence cited is derived from in vitro or animal studies; fewer human experiments are included in those studies.

Although there has already shown great results in current studies, there are still several aspects and areas that need further investigation and research. One limitation shown here is that many

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experiments included in the studies have been conducted only in laboratory settings or on animal models rather than really try on human and see how human body will react. More clinical research involving human participants would really help researchers better understand how these methods affect skin aging in real-life conditions. Another challenge that shown in these studies is that there lack of consistent methods for exosomes isolation and characterization, which can make it difficult when comparing different methods in various studies. Future researchers may find alternative ways that could help improve exosome performance. Finally, additional human model trial will definitely be important for evaluating the methods' safety and efficacy. Based on the evidence included in this paper, stem cell-derived exosomes have huge potential in skin anti-aging research and may contribute to future developments in medicine.

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